UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,778	07/27/2006	Zhonglin Chai	2354/370	7943

26774 7590 05/27/2009

NIXON PEABODY LLP - PATENT GROUP
1100 CLINTON SQUARE
ROCHESTER, NY 14604

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,778	CHAI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/4/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed April 16, 2009, is acknowledged.

2. Claims 10 and 33-35 are pending and under examination in the instant application.

3. Applicant's IDS, filed 11/04/08, is acknowledged.

4. The following new ground of rejections are necessitated by the amendment submitted April 16, 2009.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 10 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a method for treating or "preventing cell division autoantigen-1 (CDA1) modulated renal fibrosis", the fibrosis resulting from diabetes, the method comprising: administering to a subject in need thereof a therapeutically or "prophylactically" effective amount of an AT 1 receptor antagonist, wherein the administration of the AT 1 receptor antagonist reduces the expression or activity of CDA1 in a kidney cell of the subject, the administration leading to a decrease in the expression of an extracellular matrix protein in a kidney of the subject, thereby "treating or preventing the CDA1 modulated renal fibrosis resulting from diabetes", wherein the AT1 receptor antagonist is valsartan in claim 33, wherein the subject is a mammal in claim 34, wherein said administering is carried out to "treat CDA1 modulated renal fibrosis resulting from diabetes". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous office Action mailed 10/16/08.

Applicant's arguments, filed 4/16/09, have been fully considered, but have not been found convincing.

Applicant argues that in establishing a causal connection between the increase in CDA1 expression and fibrosis, the applicants have also demonstrated a concomitant increase in the expression of extracellular matrix proteins such as fibronectin and collagen IV (see Figures 4A to 4D). Given that it was well accepted at the priority date that fibrosis is caused by the excessive secretion of extracellular matrix proteins, persons of skill in the art would have expected from this data that fibrosis could be treated or prevented by decreasing the expression of extracellular matrix proteins in the kidney of a subject.

It will be appreciated that fibrosis could logically be prevented by maintaining low levels of CDA1 in a cell, given that low levels of CDA1 will result in the decreased expression of extracellular matrix proteins. Similarly, an existing fibrosis could be prevented from advancing to a more serious condition by limiting the expression of CDA1.

It will be further appreciated that an existing fibrosis may be reversed by the present invention. The level of extracellular matrix protein in a tissue is controlled by the rate of synthesis of the protein offset by the rate of degradation. Extracellular matrix proteins will naturally degrade over time. In many instances the degradation is actively progressed by the action of various proteases resident in the interstitial space. Thus, where the level of CDA1 is maintained at a low level, the rate of protein degradation can be greater that the rate of synthesis thereby leading to a net decline in the level of extracellular protein.

However, while Applicant discloses in specification the scientific theory underlying his invention. However, the scientific theory is very general and does not render the invention predictable. The influence of a scientific theory should depend on its empirical and demonstrable aspects and not its underlying logic. Yet such empirical and demonstrable aspects of the claimed methods with the AT1 receptor antagonist are lacked in the instant specification. It is not clear that the skilled artisan could predict the efficacy of the AT1 receptor antagonist, encompassed by the claims. It is not clear that the effect of the AT1 receptor antagonist is directly affecting the renal fibrosis resulting from diabetes through reducing the expression or activity of CDA1 in the kidney. The specification fails to provide empirical data to show that the claimed method would work *in vivo*.

On the basis of the disclosed co-localization of CDA1 expression with fibrosis in the remnant kidney following subtotal nephrectomy observation alone (see page 7, lines 12-13), applicant concludes that the scope of the a compound that modulate the expression and/or activity of a CDA encompassed by the claimed invention can have biological activity to treat or prevent a condition related to synthesis of an ECM protein including kidney fibrosis and be provided as pharmaceutical compositions to subjects including human to effectively treat/prevent fibrosis including kidney fibrosis. The specification contemplated that Angiotensin II antagonist such as an AT-1 receptor antagonist, e.g., valsartan, or TGFβ antagonist or CTGF antagonist can be used to treat/prevent a condition related to synthesis of an ECM protein (fibrosis disorder). No such agents were produced or tested, it is unclear if these assay results are predictive of treating or preventing a condition related to synthesis of an ECM protein.

Applicant points to Drs. Zhonglin Chai and Emmanuel Cooper declaration under , 37 CFC 132, filed 4/16/09 to support the contention that one skill in the art would have been fully aware of and able to adopt the dosage protocols of any clinically available AT1 receptor antagonist as unsed in the treatment of hypertension. Applicant contends that the soundness of applicant's position is confirmed by Dr. Cooper who was working in the field of diabetes research and clinical practice at the priority date. However, the Zhonglin Chai and Emmanuel Cooper declaration under , 37 CFC 132, filed 4/16/09 are insufficient to overcome the 112 (1^{st}) enablement rejection because the declaration is viewed as statements of opinions because there does not appear to be any evidence of the use, as claimed, of the an AT1 receptor antagonist to treat or prevent cell division autoantigen-1 (CDA1) modulated renal fibrosis resulting from diabetes.

Applicant fails to address the issue of "preventing/prophylactic", the rejection is reiterated here again. The burden of enabling the prevention of a disease (i.e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those mammals susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to kidney fibrosis resulting form diabetes within the scope of the presently claimed invention. Nor is sufficient guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed modulating the expression and/or activity of a CDA in preventing fibrosis.

8. Claims 10 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments, filed 4/16/09, have been fully considered, but have not been found convincing.

Applicant addresses only the CDA1 issue, but fails to address the AT1 receptor antagonists to prevent increased CDA1 expression.

There is no described or art-recognized correlation or relationship between the structure of the invention, an AT1 receptor antagonist and it's CDA1 expression or activation reduction, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of AT1 receptor antagonists, which retain the features essential to the instant invention.

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 10 and 33-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Kelly et al (Kidney International. 2002, 61:31-39).

Kelly et al teach that treatment of diabetic Ren-2 rats with valsartan (20mg/kg/day) reduced apoptosis to control levels and a reduction in TGF-β1 gene expression to that of control. Kelly et al concluded that tubular apoptosis is a prominent feature of diabetic Ren-2 rats that is attenuated by blockage of the RAS in association with modulation of pro- and anti-apoptotic growth factor expression (see abstract in particular). Kelly et al teach that tubulointerstitial injury, characterized by interstitial fibrosis and tubular atrophy is a major feature of most renal diseases including diabetic nephropathy (see page 31, 1st col., 1st ¶). Kelly et al teach that the diabetic Ren-2 rat associated with significant tubulointerstitial fibrosis and tubular epithelial cell apoptosis, but renoprotective therapy with RAS blockade ameliorated this mode of cell loss (i.e., treating diabetic renal fibrosis with valsartan) (see page 36, 2nd col., top ¶ and table 4).

While the prior art teachings may be silent as to the "treating or preventing the cell division autoantigen-1 (CDA1) modulated renal fibrosis" per se; the method, the product used in the reference method are the same as the claimed method. Therefore "treating or preventing the cell division autoantigen-1 (CDA1) modulated renal fibrosis" is considered inherent properties.

The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which a particular AT1 receptor antagonist alleviates symptoms of renal fibrosis resulting from diabetes does not appear to distinguish the prior art teaching the same methods to achieve the same end-result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

The reference teaching anticipates the claimed invention.

11. Claims 10 and 33-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilkinson-Berka et al (Nephrol Dial Transplant (2001) 16:1343-1349).

Wilkinson-Berka et al teach that renoprotective and anti-hypertensive effects of combined valsartan and perindopril in progressive diabetic nephropathy in the transgenic (mRen-2)27 rat.

Wilkinson-Berka et al teach the use of monotherapy with angiotensin type 1 (AT1) receptor blockade valsartan (V, 20 mg/kg/day) in progressive diabetic nephropathy in the transgenic (mRen-2)27 rat. Wilkinson-Berka et al teach that systolic blood pressure was lowered with all treatments, but greater reductions were observed with valsartan (V) monotherapy. All treatments reduced albuminuria, the decline in glomerular filtration rate, and cortical collagen staining, to the same extent. The glomerulsclerotic index was increased with diabetes and reduced with valsartan monotherapy (see abstract in particular). Wilkinson-Berka et al teach that the tubulointerstitium of both the kidney cortex and medulla, increased collagen and inflammatory cells were observed in diabetic Ren-rate compared to non-diabetic controls (by definition, renal fibrosis in a diabetic model) (see page 1346, bridging ¶). Table 1 shows that treatment with valsartan reduced cortical collagen staining in diabetic Ren 2 rats compared to non-diabetic controls. The renal diabetic fibrosis is relevant to the Wilkinson-Berka et al study teaches that the deterioration in renal structure and function associated with the progresion of diabetes can be improved by blockade of the renin-angiotensin system (RAS), with angiogtensisn type 1 (AT1) receptor blocker (see page 1343 under Introduction). mRNe-2)27 rat displays sever glomerulosclerosis, tubulointerstitial disease and a decline in renal function (see page 1344, 1st col., 2nd ¶).

While the prior art teachings may be silent as to the "treating or preventing the cell division autoantigen-1 (CDA1) modulated renal fibrosis" per se; the method, the product used in the reference method are the same as the claimed method. Therefore "treating or preventing the cell division autoantigen-1 (CDA1) modulated renal fibrosis" is considered inherent properties.

The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which a particular AT1 receptor antagonist alleviates symptoms of renal fibrosis resulting from diabetes does not appear to distinguish the prior art teaching the same methods to achieve the same end-result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

The reference teaching anticipates the claimed invention.

12. Claims 10 and 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Remuzzi et al (J. Am. Soc. Nephrol. 1993, 4:40-49).

Remuzzi et al teaches the use of losartan (Angiotensin II receptor blocker, specific for AT1 receptors) with experimental diabetes. Losartan treatment prevented GFR rise. Losartan significatnly prevented proteinuria and glomerulosclerosis and showed an important increase in

the filtration. Remuzzi et al teach that the results presented strongly indicate that reduction of all activity plays a crucial role in the preservation of glomerular structure and function and suggest that the favorable effects previously observed with angiotensin-converting enzyme inhibition in this model depend directly on the reduction of all activity (see abstract). Remuzzi et al teach that Interstitial fibrosis and inflammation (renal fibrosis caused by diabetes) were graded from 0 to 4+ (see page 43, 1st col., top ¶). Remuzzi et al teach that after 1 yr, sings of interstitial fibrosis or inflammation were observed in these animal in four control rats out of eight, however, the interstiatial fibrosis and inflammation were significantly higher in diabetic rats than control. Importantly, in diabetic rates treated with losartan, the interstitial inflammation were limited (treating renal fibrosis resulting from diabetes with losartan) (see page 46, 2nd col., 1st ¶).

While the prior art teachings may be silent as to the "treating or preventing the cell division autoantigen-1 (CDA1) modulated renal fibrosis" per se; the method, the product used in the reference method are the same as the claimed method. Therefore "treating or preventing the cell division autoantigen-1 (CDA1) modulated renal fibrosis" is considered inherent properties.

The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which a particular AT1 receptor antagonist alleviates symptoms of renal fibrosis resulting from diabetes does not appear to distinguish the prior art teaching the same methods to achieve the same end-result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

The reference teaching anticipates the claimed invention.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 22, 2009

/Maher M. Haddad/
Maher M. Haddad, Ph.D.
Primary Examiner
Technology Center 1600